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LETTER TO THE EDITOR

Safety and efficacy of BAY 94–9027, an extended-half-life factor VIII, during minor surgical procedures in patients with severe haemophilia A

In patients with haemophilia A, minor surgical interventions are vital for improving well-being and may prevent major surgical procedures. However, the risk of bleeding in minor surgery may be higher than in major surgery. Local haemostasis may not be ensured with suturing, cautery or pressure application, and minor procedures may be performed without the involvement of an experienced multidisciplinary team.[1]

Individualised haemostatic therapy should be used to maintain appropriate levels of factor VIII (FVIII) in haemophilia A patients during the perioperative period for all surgical procedures to prevent excessive bleeds. However, FVIII monitoring is seldom performed during minor surgeries, warranting prior knowledge of FVIII products.

BAY 94–9027 (damoctocog alpha pegol; Jivi®; Bayer AG, Leverkusen, Germany) is a B-domain-deleted, recombinant FVIII (rFVIII) site-specifically conjugated to a 60-kDa polyethylene glycol, approved for previously treated patients, ≥12 years of age with haemophilia A. The pharmacokinetic properties of BAY 94–9027, including an increased area under the curve and longer half-life compared with standard-half-life (SHL) rFVIII products, reduce dosing intervals and facilitate individualisation of prophylaxis.[2,3] BAY 94–9027 has been shown to be efficacious and well tolerated in patients with severe haemophilia A undergoing major surgeries.[4] Extended half-life (EHL) rFVIII products such as BAY 94–9027 could benefit patients undergoing outpatient procedures maintain haemostasis for longer period and stable FVIII plasma levels until wounds are healed, compared with SHL rFVIII products.[4] We report the interim efficacy and safety results of BAY 94–9027 for the prevention of bleeds in adult, adolescent and paediatric male patients with previously treated severe haemophilia A (FVIII <1%) undergoing minor surgeries during the PROTECT VIII (NCT01580293; a phase 2/3 study, involving adolescents and adults) or PROTECT VIII Kids (NCT01775618; a phase 3 study, involving patients <12 years) clinical trials, with a cut-off date for data collection of 15 February 2017.

Both studies included BAY 94–9027 infusions administered on-demand or as prophylaxis dosed twice weekly (PROTECT VIII 30–40 IU/kg, PROTECT VIII Kids 25 IU/kg), every 5 days (PROTECT VIII 45–60 IU/kg, PROTECT VIII Kids 45 IU/kg) or every 7 days (both 60 IU kg^{-1}).[3,5] Minor surgeries included the following: any surgical procedure in which the overall bleeding risk is low, not routinely done under general anaesthesia in an individual without a bleeding disorder; with no penetration into, or exposure of, a major body cavity; and no potential to result in substantial impairment of physical or physiologic functions. Most of the minor surgeries included were dental extractions, incision and drainage of abscess, or simple excisions.

The efficacy of BAY 94–9027 in providing bleeding control during minor surgery was primarily based on each surgeon's assessment of haemostasis compared with an expectation in patients without haemophilia undergoing comparable procedures. A 4-point scale was used to assess haemostasis based on blood loss: 'excellent' (blood loss less than expected), 'good' (as expected), 'moderate' (more than expected) or 'poor' (uncontrolled bleeding). Estimated blood loss during surgery and the need for blood transfusion during the perioperative period were also reported as clinical confirmation of the physician assessment of haemostasis. The primary safety outcome for this study was the occurrence of intraoperative complications secondary to bleeding. Adverse event reporting and FVIII inhibitor measurements were continuously performed during the studies.[3,5] Additionally, the number of BAY 94–9027 infusions and the dose applied during the pre- and postoperative periods are reported to assess the intensity of treatment.

Thirty-six adolescent and adult and five paediatric patients were included in this interim analysis. Median age (range) was 38.5 (12–62) years and 4.0 (2–8) years in PROTECT VIII and PROTECT VIII Kids studies, respectively; most patients were receiving BAY 94–9027 as regular prophylaxis every 5 or 7 days (Table 1). In total, 69 minor surgeries were performed on 41 patients: 62 in adults and adolescents and 7 in children. Most (n = 45; 65.2%) were dental procedures. Others included seven (10.1%) orthopaedic, seven (10.1%) dermatologic, four (5.8%) ophthalmologic and six 'other' (8.7%) procedures (Table 2).

Intraoperative adequacy of haemostasis was available for 57 of 69 procedures and was rated 'good' (n = 32 [56.1%]) or 'excellent' (n = 25 [43.9%]). Blood loss was absent or ≤10 ml in all cases except

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[Correction added on 24 August 2021, after first online publication: The copyright line was changed.]

TABLE 1 Demographic and baseline characteristics of patients undergoing minor surgical procedures

	PROTECT VIII (*n* = 36)	PROTECT VIII Kids (*n* = 5)
Race, *n*[a] (%)		
White	25 (69)	3 (60)
Asian	7 (19)	2 (40)
Black	1 (3)	0
Not reported	3 (8)	0
Age at enrolment, y; mean ± SD	37.6 ± 15.1	4.6 ± 2.4
Baseline weight, kg; mean ± SD	76.0 ± 18.8	20.1 ± 8.3
BAY 94–9027 treatment regimen, *n* (%)[a]		
On-demand	4 (11)	–
Prophylaxis 2×W	6 (17)	0 (0)
Prophylaxis E5D	8 (22)	3 (60)
Prophylaxis E7D	18 (50)	2 (40)

Abbreviations: 2×W, twice weekly; E5D, every 5 days; E7D, every 7 days.

[a]At randomisation.

for 1 forearm angioma ablation and 1 perianal abscess drainage, where blood losses were 20 ml and 100 ml (the volume measured during abscess drainage included purulent secretion), respectively. No transfusions were required; no haemostasis-related surgical complications or FVIII inhibitors were reported.

Overall, 23/69 (33.3%) procedures were performed without perioperative infusions besides regular prophylaxis treatment, including 14 dental procedures. Most (*n* = 21, 91%) of these were performed on the day of patients' scheduled prophylaxis infusions, at their regular prophylactic dose. Out of the 23 procedures, 10 (43%) were performed on patients receiving every 5-day or every 7-day prophylaxis regimen.

In the remaining 46 procedures, dose and frequency of infusions applied due to surgery were individualised. The mean ± SD total dose for the minor surgery was 62.1 ± 62.7 (median [range], 43.5 [16.7–336.2]) IU/kg. Only 9 surgeries required more than 1 infusion (Table 2); the number of infusions ranged from 2 to 10, with a median (Q1; Q3) time between infusions of 23.72 h (22.85; 27.85). Thirteen (28%) of these procedures were performed on patients treated on demand. For the remaining 33 procedures with perioperative infusions, 5 (15%) were performed on the day of the prophylaxis, and 19 (57%) were performed in patients receiving every 5-day or every 7-day prophylaxis regimen.

In 21/26 (81%) of all procedures performed on the day of the scheduled prophylaxis infusion, the patients did not receive any additional infusions. By contrast, additional infusions were administered in 28/30 (93%) of procedures performed 1–7 days after patients' previous prophylaxis infusions.

Antifibrinolytic agents, including tranexamic acid and aminocaproic acid, were used in 17/69 (24.6%) minor surgeries performed during both PROTECT VIII trials. Tranexamic acid was used during 16 (23.2%) procedures (dental [*n* = 14], other [*n* = 1], ophthalmologic [*n* = 1]). Aminocaproic acid was used during one (1.4%) dental procedure. Tranexamic acid was used on its own in four (17.4%) dental procedures performed without additional infusions besides regular prophylaxis treatment.

To our knowledge, this is the largest study investigating an EHL rFVIII compound in the minor surgery settings. In this subset of 41 adult, adolescent and paediatric patients in the PROTECT VIII and PROTECT VIII Kids clinical trials, haemostasis was rated as 'good' or 'excellent' during all rated procedures, minimal blood loss was reported, and no bleeding complications were observed during the intra- or postoperative period (Table 2). One patient received 10 daily infusions during and after an emergency incision and drainage of a perianal abscess (Table 2), including one perioperative infusion and nine postoperative infusions. The perioperative infusion was administered to maintain adequate FVIII levels during the procedure. The postoperative infusions were administered to prevent bleeding. The patient did not experience any postoperative blood loss; the number of infusions was not determined by bleeding complications or low FVIII plasma levels. Infusions were applied until the wound healed in the absence of FVIII level monitoring.

This is consistent with earlier, smaller studies investigating other EHL rFVIII compounds in this setting that also reported clinically meaningful haemostatic control. For example, studies of efmoroctocog alfa[6] and rurioctocog alfa pegol[7] reported excellent or good haemostatic efficacy in 32 and 4 minor surgical procedures, respectively, and these treatments were well tolerated. Nevertheless, higher total doses per minor surgery were reported for rurioctocog alfa pegol.[6,7]

The main limitation of this interim analysis is the lack of standardised definitions for minor surgery in people with haemophilia, potentially hindering interpretation of surgical outcomes across clinical trials.[8] Different criteria for minor surgeries have been included in studies in haemophilia, including 'procedures requiring only skin excision or small sutures',[9] 'surgeries which can be safely and comfortably performed on a patient who has received local or topical anaesthesia, with minimal preoperative medication or intraoperative sedation',[7] and 'any surgical procedure that did not involve general anaesthesia and/or respiratory assistance'.[10] Nevertheless, here, BAY 94–9027, an EHL rFVIII with the potential for less frequent infusions and reduced factor consumption, showed a good safety profile and could prevent bleeds in adult, adolescent and paediatric patients undergoing minor surgeries.

These interim data from the two PROTECT VIII studies suggest that most patients on prophylaxis with BAY 94–9027 who require minor surgeries can be managed effectively by performing the required procedure under adequate FVIII coverage provided by their regular prophylaxis dosing, or with an additional single infusion during the perioperative period. They also show that scheduling an operation for a day of the patient's regular prophylactic infusion may make additional perioperative infusions unnecessary. Moreover, there were no haemostasis-related complications with BAY 94–9027 during any of the minor surgeries. These data support the use of BAY 94–9027 before, during and after minor surgeries. Due to its extended half-life, BAY 94–9027 can maintain longer stable FVIII plasma levels compared with SHL rFVIII products. In conclusion,

TABLE 2 Details of minor surgical procedures performed under treatment with BAY 94–9027

Type of surgery (number of procedures)	Blood loss during surgery, mL	Assessment of haemostasis during surgery	Number of study–drug infusions administered (number of surgeries)
PROTECT VIII			
Dental (*n* = 42)[a]	0 (*n* = 35)	Good (*n* = 25)	0 (*n* = 13)
	1–10 (*n* = 7)	Excellent (*n* = 11)	1 (*n* = 25)
		NA (*n* = 6)	2 (*n* = 3)
			8[b] (*n* = 1)
Orthopaedic (*n* = 7)[c]	0 (*n* = 6)	Good (*n* = 2)	0 (*n* = 4)
	1–10 (*n* = 1)	Excellent (*n* = 1)	1 (*n* = 3)
		NA (*n* = 4)	
Dermatologic (*n* = 5)[d]	0 (*n* = 5)	Good (*n* = 1)	0 (*n* = 3)
		Excellent (*n* = 4)	1 (*n* = 2)
Ophthalmologic (*n* = 3)[e]	0 (*n* = 3)	Good (*n* = 2)	0 (*n* = 2)
		Excellent (*n* = 1)	1 (*n* = 1)
Other (*n* = 5)[f]	0 (*n* = 3)	Good (*n* = 1)	1 (*n* = 1)
	1–10 (*n* = 1)	Excellent (*n* = 3)	2 (*n* = 1)
	100 (*n* = 1)	NA (*n* = 1)	3 (*n* = 1)
			6 (*n* = 1)
			10[g] (*n* = 1)
PROTECT VIII Kids			
Dental (*n* = 3)[a]	0 (*n* = 1)	Good (*n* = 1)	0 (*n* = 1)
	1–10 (*n* = 2)	Excellent (*n* = 1)	1 (*n* = 2)
		NA (*n* = 1)	
Dermatologic (*n* = 2)[d]	0 (*n* = 1)	Excellent (*n* = 2)	1 (*n* = 2)
	20 (*n* = 1)		
Ophthalmologic (*n* = 1)[e]	1	Excellent	1 (*n* = 1)
Other (*n* = 1)[f]	0	Excellent	2 (*n* = 1)
Number of procedures with additional[h] BAY 94–9027 infusions administered, *n*/*N* (%)			46/69 (66.7)
Number of procedures without additional[h] BAY 94–9027 infusions administered, *n*/*N* (%)			23/69 (33.3)

Abbreviation: NA, not available.

[a]Dental procedures included in PROTECT VIII and PROTECT VIII Kids, respectively: tooth extraction (*n* = 24; *n* = 3), dental scale and polish (*n* = 13; *n* = 0), dental crown treatment (*n* = 3, *n* = 0), root canal treatment (*n* = 1, *n* = 0) and dental restoration (*n* = 1, *n* = 0).

[b]No additional data are available for this patient who underwent a tooth extraction; however he did not experience bleeding during or after the procedure and maintained a good level of haemostasis.

[c]Orthopaedic procedures included in PROTECT VIII: knee aspiration (*n* = 4), arthrocentesis (*n* = 1), knee geniculate nerve block (*n* = 1) and needle aspiration for suspected bacterial infection (*n* = 1). No orthopaedic procedures were performed during PROTECT VIII Kids.

[d]Dermatologic procedures included in PROTECT VIII and PROTECT VIII Kids, respectively: basocellular carcinoma ablation (*n* = 2, *n* = 0), Mohs surgery for basal cell carcinoma (*n* = 1, *n* = 0), removal of skin carcinoma (*n* = 1, *n* = 0), shave biopsy of intradermal nevus (*n* = 1, *n* = 0), ablation of earlobe angioma (*n* = 0, *n* = 1) and ablation of forearm angioma (*n* = 0, *n* = 1).

[e]Ophthalmologic procedures included in PROTECT VIII and PROTECT VIII Kids, respectively: laser surgery of anterior lens capsule (*n* = 2, *n* = 0), cataract removal (*n* = 1, *n* = 0) and eyelid lesion biopsy (*n* = 0, *n* = 1).

[f]Other procedures included in PROTECT VIII and PROTECT VIII Kids, respectively: incision and drainage of perianal abscess (*n* = 2, *n* = 0), colonoscopy (*n* = 1, *n* = 0), repeat vasectomy (*n* = 1, *n* = 0), orchidopexy and port-a-cath removal (*n* = 0, *n* = 1), and frenulum excision (*n* = 1, *n* = 0).

[g]The patient underwent an emergency incision and drainage of a perianal abscess and received one peri- and nine postoperative infusions with BAY 94–9027. He did not experience any blood loss during the postoperative period and the number of infusions was not driven by bleeding complications or low plasma FVIII levels; it was estimated to prevent perioperative and postoperative bleeding. Daily FVIII infusions were applied until the wound fully healed.

[h]Infusions administered in addition to regular prophylaxis.

BAY 94–9027 could allow fewer infusions during the perioperative period, therefore simplifying the management of patients undergoing minor surgeries.

KEYWORDS

clinical outcome, clinical trials, extended half-life, factor VIII, haemophilia A, minor surgery, PEGylation

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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